

**A PROSPECTIVE STUDY OF ESOPHAGEAL  
VARICEAL RECURRENCE AND REBLEED RATES  
AFTER PRIMARY ERADICATION**

*Dissertation Submitted in partial fulfillment of the  
regulations for the award of the degree of*

**BRANCH – IV D.M.  
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THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY  
CHENNAI**



**GOVERNMENT STANLEY MEDICAL COLLEGE,  
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CHENNAI  
AUGUST 2008**

## **DECLARATION**

I, **Dr. R.SELVA SEKARAN**, solemnly declare that dissertation titled, “**A PROSPECTIVE STUDY OF ESOPHAGEAL VARICEAL RECURRENCE AND REBLEED RATES AFTER PRIMARY ERADICATION**” is the bonafide work done by me at Govt. Stanley Medical College and Hospital during the period January 2006 to March 2008 under the expert guidance and supervision **Prof. V.Jayanthi, M.D.D.M.**, Head of the Department, Department of Medical Gastroenterology.

The dissertation is submitted to the **Tamil Nadu Dr. MGR Medical University** towards partial fulfillment of requirement for the award of **D.M Degree (Branch IV) in Medical Gastroenterology**.

Place : Chennai

Date : 02.06.08

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# **CERTIFICATE**

This is to certify that this dissertation entitled “**A PROSPECTIVE STUDY OF ESOPHAGEAL VARICEAL RECURRENCE AND REBLEED RATES AFTER PRIMARY ERADICATION**” is a bonafide original work of **Dr. R. Selva sekaran** in partial fulfillment of the requirement for **D.M (Branch IV) Medical Gastroenterology** examination of the Tamil Nadu Dr.MGR Medical University to be held in August 2008.

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# INTRODUCTION

Bleeding from esophageal varices is the leading cause of death in patients with portal hypertension, with a mortality of up to 50% for the initial bleed and 30% for subsequent bleeds (1-4). Endoscopic variceal sclerotherapy (EST) has been widely used in the emergency treatment of patients with actively bleeding esophageal varices (5-12). Even though the initial bleed may effectively be controlled by sclerotherapy, the risk of subsequent rebleeding is substantial (13-18).

There is a general consensus that patients surviving a bleed episode should be treated to prevent rebleeding (19-21). Considerable evidence has supported the use of repeated sclerotherapy to obliterate esophageal varices to prevent further variceal bleeding (22-27). While undergoing sclerotherapy before eradication, patients may continue to have variceal bleeds (28). Repeated injection also increases the cumulative risk of developing complications in patients (29, 30).

Endoscopic variceal ligation (EVL), is widely used, may provide safer and quicker eradication of varices (31, 32). However, no long-term data for recurrent bleeding after variceal eradication by ligation exists and there is a concern that rebleeds may be higher after ligation than after sclerotherapy (33). The cost and affordability by the patient has resulted in selective use of EVL when compared to EST which is cheaper and readily available in all centers in the Indian subcontinent. Also a recent study from the our Institution has highlighted the natural history of oesophageal varices in an era of sclerotherapy (34). The rebleed rate was 29.4 %.

Despite the previous widespread use of endoscopic sclerotherapy, accurate data on long-term recurrence and rebleeding after variceal eradication and the need and optimal frequency of endoscopic surveillance are scant (35).

**Hypothesis:**

Eradication of esophageal varices by repeated injection sclerotherapy and maintenance of eradication using continued surveillance endoscopy may reduce recurrent variceal bleeding and death from esophageal varices.

Ethics committee approval was obtained from the institution before initiating the study



## **AIM**

This present study aimed to evaluate prospectively the overall long-term clinical outcome in terms of recurrence of varices and rebleed rates after eradication of varices following EST in consecutively treated cirrhotic patients with bleeding esophageal varices.

# REVIEW OF LITERATURE

Portal hypertension represents an increase of the hydrostatic pressure within the portal vein or its tributaries and is defined as an increase in the pressure gradient between the portal vein and hepatic veins or inferior vena cava.

In portal hypertension, blood that normally flows through the liver is diverted into systemic veins because of increased resistance to portal venous flow. This diversion of portal venous blood occurs via exiting portosystemic communications (eg, coronary vein) and the opening of embryonic channels (eg, paraumbilical veins). The most common portosystemic anastomosis is via the coronary-gastroesophageal route, which occurs in 80-90% of patients and gives rise to lower esophageal and gastric varices.

## **Anatomy of the portal venous system:**

The portal venous system includes all veins that carry blood from the abdominal part of the alimentary tract, spleen, pancreas, and gallbladder. The union of the superior mesenteric and splenic veins forms the portal vein posterior to the pancreatic head. The portal vein enters the liver at the porta hepatis and soon divides into left and right portal vein branches. When portal circulation is obstructed, a remarkable collateral circulation develops, redirecting portal venous blood into systemic veins.

## **Collateral circulation:**

Portosystemic collaterals are classified into 4 main groups as follows:

- Group I has 2 divisions.
  - Group I a: At the cardia of the stomach, the left gastric (coronary) vein and short gastric veins of the portal venous system anastomose with the intercostal veins, diaphragmatic veins, esophageal veins, the azygos vein, and other minor systemic veins of the caval

system (such as the lumbar veins). Diversion of blood into these channels leads to the development of submucosal esophageal and gastric varices.

- Group I b: At the anus, the superior hemorrhoidal vein of the portal system anastomoses with the middle and inferior hemorrhoidal veins of the caval system. Diversion of blood into these channels may lead to the formation of internal hemorrhoids.
- Group II: In the falciform ligament, blood flows through the paraumbilical veins (remnants of umbilical circulation of the fetus).
- Group III: Collaterals occur where intraperitoneal organs are in contact with retroperitoneal tissues or adherent to the abdominal wall. These collaterals include veins from the liver to the diaphragm, veins in the lienorenal ligament and the omentum, lumbar veins, and veins developing in previous laparotomy scars.
- Group IV: Portal venous blood is carried to the left renal, inferior phrenic, and left adrenal veins directly from the splenic vein or via the diaphragmatic, pancreatic, left adrenal, or gastric veins. Esophageal varices are associated with hepatopulmonary syndrome, and anastomoses between the portal veins and pulmonary veins have been found in both animals and humans. With increasing portal venous pressure, the mediastinal veins enlarge, enhancing their likelihood of draining into the pulmonary veins via the pleural veins.

Spontaneous splenorenal shunts are seen in 10-20% of patients with PHT. Blood from gastroesophageal collaterals and retroperitoneal and venous systems of the abdomen ultimately reaches the superior vena cava via the azygos or hemiazygos system. A small volume of blood enters the IVC.

The collateral pathways in extrahepatic venous obstruction depend on the site of obstruction. In the absence of liver disease, with splenic vein occlusion, portal-portal collateral pathways develop over gastric veins (splenic, short gastric, coronary portal veins) and omental veins (splenic, gastroepiploic or arch of Barkow, superior mesenteric portal veins). In superior mesenteric vein obstruction, collaterals

develop via the pancreaticoduodenal or cystic veins. In portal vein occlusion, collaterals develop via peribiliary venous plexus, via veins in the hepatoduodenal ligament, and in the hepatic hilus.

The following four zones of venous drainage are involved in the formation of gastroesophageal varices (36).

The gastric zone is 2 to 3 cm below the gastroesophageal junction, where the veins meet at the upper end of the cardia of the stomach, drain into short gastric and left gastric veins, and then drain into the splenic and portal veins, respectively.

The palisade zone is 2 to 3 cm proximal to the gastric zone into the lower esophagus, where the veins communicate with extrinsic (periesophageal) veins in the distal esophagus. This zone forms the dominant watershed area between the portal and the systemic circulations.

More proximal to the palisade zone in the esophagus is the perforating zone, where a network of submucosal veins in the esophagus connects to the periesophageal veins, which drain into the azygous system and subsequently into the systemic circulation.

The truncal zone is approximately 10 cm in length and is located proximally to the perforating zone in the esophagus. It typically has four longitudinal veins in the lamina propria.

### **Hemodynamic principle:**

Portal hypertension is a pathologic increase in the portal venous pressure gradient between the portal vein and the inferior vena cava. It results from changes in portal resistance together with changes in portal inflow, as defined by Ohm's law:

$$P(\text{pressure}) = Q(\text{blood flow}) \times R(\text{resistance})$$

The mechanism of the increase in portal pressure depends on the site and the cause of portal hypertension, cirrhosis being the most common cause in the Western world (37). The initial event in

the development of portal hypertension in cirrhosis is an increase in resistance to outflow from the portal venous bed. This results from a relatively fixed component from distortion of the intrahepatic vascular bed from the disruption of hepatic architecture and a dynamic component from impaired intrahepatic vasodilation. An estimated 30% of the increased portal resistance is due to the hemodynamic changes, characterized by hepatic vasoconstriction and impaired response to vasodilatory stimuli (38, 39). An intrahepatic decrease in the production of the vasodilator nitrous oxide (NO) (40), in combination with an increase in the production of the vasoconstrictor endothelin-1, is the major contributor to the dynamic increase in hepatic vascular resistance (41, 42).

Cirrhosis is associated with a hyperdynamic circulatory state that is characterized by peripheral and splanchnic vasodilation, reduced mean arterial pressure, and increased cardiac output. NO-mediated splanchnic vasodilatation produces an increase in inflow of systemic blood into the portal circulation, which causes an increase in portal pressure (43).

Portal pressure is most commonly determined by the hepatic vein pressure gradient (HVPG), which is the difference between the wedged hepatic venous pressure (reflecting the hepatic sinusoidal pressure) and free hepatic vein pressure (44, 45). In combination with venography, right-sided heart pressure measurements, and transjugular liver biopsy, measurement of the HVPG usually delineates the site of portal hypertension (ie, presinusoidal, sinusoidal, or postsinusoidal).

Varices form only when the HVPG exceeds 10 mm Hg and bleed only when the HVPG exceeds 12 mm Hg (36,50). Not all patients who have a HVPG greater than 12 mm Hg bleed. Other local factors that increase variceal wall tension are required. The wall tension is defined by Frank's modification of Laplace's law (46):

$$T = (P_{\text{varices}} - P_{\text{esophageal lumen}}) \times (\text{radius of varix}) / \text{wall thickness}.$$

The varix ruptures when the tolerated wall tension is exceeded because the variceal wall thins and the varix increases in diameter and has an increased pressure. Larger varices at sites of limited soft tissue support, notably the gastroesophageal junction, are at greater risk for variceal rupture and bleeding in patients who have portal hypertension.

### **Etiology of portal hypertension:**

The causes of PHT are many and can be subdivided into diseases causing prehepatic, hepatic (presinusoidal, sinusoidal and postsinusoidal), or posthepatic PHT

Causes of portal hypertension

- **Presinusoidal**
  - Prehepatic
    - Portal vein thrombosis
    - Superior mesenteric vein thrombosis
    - Sinistral portal hypertension (splenic vein thrombosis)
  - Intrahepatic
    - Idiopathic portal hypertension
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
- **Sinusoidal**
  - Cirrhosis
  - Vitamin A toxicity

- Infiltrative disorders (eg, lymphoproliferative and myeloproliferative diseases)
- **Post-sinusoidal**
  - Venous-occlusive disease
  - Budd Chiari syndrome
  - Congenital malformation (web & diaphragm) and thrombosis of the IVC
  - Congestive heart failure

### **Clinical presentation:**

PHT is accompanied by 3 major complications, as follows:

- Gastrointestinal tract hemorrhage
- Ascites
- Encephalopathy

Hepatic encephalopathy is devastating and usually results from gastrointestinal bleeding, which is life threatening. The development of hepatic encephalopathy in patients with portal hypertension is most often related to the size of the portosystemic anastomosis. Splenoportal shunts are usually large. Stigmata of cirrhosis, including jaundice, spider nevi, caput medusae, and palmar erythema may be associated with signs of PHT.

### **Investigation:**

Calcification in the distribution of the portal vein on a plain abdominal radiograph may indicate PHT. An upper GI tract barium series is often helpful for the detection of esophageal varices but upper gastrointestinal endoscopy is the most common method to diagnose varices.

US techniques such as duplex US or spectral Doppler imaging and CDI or power Doppler imaging are the modalities of choice in the evaluation of the liver and PHT. These techniques are noninvasive, rapid, and highly sensitive and specific.

Angiographic techniques such as SP, transhepatic portography, transumbilical catheterization, transjugular catheterization, wedge hepatic venography, and arterial portography are invasive. However, they are much more specific examinations for evaluation of PHT, and they are indicated when definitive surgery or radiologic intervention is contemplated.

The use of angiographic techniques is declining because of noninvasive imaging techniques such as US; CT and computed tomography angiography (CTA), and magnetic resonance angiography (MRA) are now available. These techniques are quickly improving and will further limit the use of angiographic methods.

SP and transumbilical catheterization is rarely performed. Arterial portography (indirect portography) and wedge hepatic venography with manometry is indicated prior to surgical portacaval shunt placement.

Carbon dioxide wedge hepatic venography is the most commonly used to visualize the portal vein before portal vein puncture for a transjugular intrahepatic portosystemic shunt (TIPS) procedure. TIPS is a radiology-guided creation of a shunt between the portal and hepatic veins in the liver by using a percutaneous transjugular approach. Because of its proven safety and effectiveness, the TIPS has largely replaced surgical decompressive shunt procedures.

### **Diagnosis of varices:**

Upper gastrointestinal endoscopy is the most common method to diagnose varices. Various criteria have been used to standardize the description of esophageal varices. The Japanese Research Society for Portal Hypertension described varices in terms of red color signs, color of the varix, form (size) of the varix, and location of the varix (47). The Northern Italian Endoscopy Club simplified this scheme by classifying varices as F1, F2, or F3 (corresponding to small, medium or large) with or without red signs. The clinically important decision is whether varices warrant therapeutic intervention. It is therefore useful to evaluate varices in terms of those that require treatment. It is recommended that



varices be classified as small, which do not always warrant intervention, or large, which include those that were previously called large (48).

Gastric varices are classified by location, which correlates with their risk of hemorrhage. Varices in direct continuity with the esophagus along the lesser and greater curves of the stomach are called gastroesophageal varices (GOV) types 1 and 2, respectively. Isolated gastric varices in the fundus (IGV1) occur less frequently than GOVs (10% versus 90%) but are the most likely to bleed. They may be caused by splenic vein thrombosis or spontaneous splenorenal collaterals.

Endoscopic ultrasound (EUS) has been used to study esophageal varices and to identify a high risk of bleeding by assessment of the cross-sectional area of varices (46); the size of and flow in the left gastric vein, azygous vein, and paraesophageal collaterals; the changes after endoscopic therapy; and the recurrence of esophageal varices after variceal ligation (collaterals >5 mm are at high risk for recurrent varices)(49). It is unclear if EUS is superior to standard endoscopy.

Esophageal capsule endoscopy is a promising modality to assess varices. It may provide an accurate, less invasive alternative to EGD for the detection of esophageal varices or portal hypertensive gastropathy. A large recent trial, reported only in abstract form, found excellent concordance with endoscopy. The role of capsule endoscopy in the management of varices is still evolving.

### **Natural history of gastroesophageal varices:**

Patients with cirrhosis and gastroesophageal varices have an HVPG of at least 10–12 mmHg (50,51). Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease; while only 40% of Child A patients have varices, they are present in 85% of Child C patients. Patients with primary biliary cirrhosis may develop varices and variceal hemorrhage early in the course of the disease even in the absence of established cirrhosis. It has also been shown that 16% of patients with hepatitis C and bridging fibrosis have esophageal varices.

Patients without varices develop them at a rate of 8% per year(52), and the strongest predictor for development of varices in those with cirrhosis who have no varices at the time of initial endoscopic screening is an HVPG >10 mmHg . Patients with small varices develop large varices at a rate of 8% per year. Decompensated cirrhosis (Child B/C), alcoholic cirrhosis, and presence of red wale marks (defined as longitudinal dilated venules resembling whip marks on the variceal surface) at the time of baseline endoscopy are the main factors associated with the progression from small to large varices.

Variceal hemorrhage occurs at a yearly rate of 5–15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices<sup>53</sup>. Other predictors of hemorrhage are decompensated cirrhosis (Child B/C) and the endoscopic presence of red wale marks (53). Although bleeding from esophageal varices ceases spontaneously in up to 40% of patients, and despite improvements in therapy over the last decade, it is associated with a mortality of at least 20% at 6 weeks (54 -56). Patients with an HVPG >20 mmHg (measured within 24 hours of variceal hemorrhage) have been identified as being at a higher risk for early rebleeding (recurrent bleeding within the first week of admission) or failure to control bleeding (83% vs. 29%) and a higher 1-year mortality (64% vs. 20%) compared to those with lower pressure(57,58). Late rebleeding occurs in approximately 60% of untreated patients, mostly within 1–2 years of the index hemorrhage.

Variceal wall tension is probably the main factor that determines variceal rupture. Vessel diameter is one of the determinants of variceal tension. At an equal pressure, a large diameter vessel will rupture while a small diameter vessel will not rupture. Besides vessel diameter, one of the determinants of variceal wall tension is the pressure within the varix, which is directly related to the HVPG. Therefore, a reduction in HVPG should lead to a decrease in variceal wall tension, thereby decreasing the risk of rupture. Indeed, variceal hemorrhage does not occur when the HVPG is reduced to <12 mmHg. It has also been shown that the risk of rebleeding decreases significantly with reductions in HVPG greater than 20% from baseline. Patients whose HVPG decreases to <12mmHg or

at least 20% from baseline levels (“HVPG responders”) not only have a lower probability of developing recurrent variceal hemorrhage, but also have a lower risk of developing ascites, spontaneous bacterial peritonitis, and death.

### **Risk factors for variceal bleeding (50):**

- Portal pressure
  - HVPG >12 mm Hg
- Varix size and location
  - Large esophageal varices
  - Isolated cluster of varices in fundus of stomach
- Variceal appearance on endoscopy ("red signs")
  - Red wale marks (longitudinal red streaks on varices)
  - Cherry-red spots (red, discrete, flat spots on varices)
  - Hematocystic spots (red, discrete, raised spots)
  - Diffuse erythema
- Degree of liver failure
  - Child-Pugh class C cirrhosis
- Presence of ascites
  - Tense ascites

### **Management of portal hypertension:**

Treatment of portal hypertension includes preventing variceal hemorrhage in patients who have never bled, treating the acute bleeding episode, and preventing rebleeding in patients who have survived a bleeding episode from esophageal or gastric varices. The main difference between these

scenarios is that natural history and prognosis are very different in each. So far, there is no effective treatment to prevent development of varices (preprimary prophylaxis) (59).

### **Prevention of first bleeding from esophageal varices:**

#### **Screening for esophageal varices:**

Current consensus is that every cirrhotic patient should be screened endoscopically for varices at time of diagnosis (60). In patients without varices on initial endoscopy, a second (follow-up) evaluation should be performed to detect the development of varices before these bleed.

Current consensus is that endoscopy should be repeated after 2 to 3 years in patients without varices at the first endoscopy (60). The expected incidence of large varices or variceal bleeding in these patients (and, thus, the risk of leaving patients without prophylaxis when it was indicated) is less than 10% at 3 years(52,61). In those centers in which hepatic hemodynamic studies are available, it is advisable to measure HVPG. An HVPG over 10 mmHg indicates a more rapid progression to complications of cirrhosis and calls for shorter surveillance intervals (59).

In patients with small varices on initial endoscopy, the aim of subsequent evaluations is to detect the progression of small to large varices because of prognostic and therapeutic implications. This will change if treatment of small varices becomes standard of practice. Based on an expected 10% to 15% per year rate of progression of variceal size, endoscopy should be repeated every 1 to 2 years in patients with small varices (60). In patients with advanced cirrhosis, red signs, or alcoholic etiology of cirrhosis, a 1-year interval might be recommended (52, 61).

### **Treatments to prevent the first esophageal bleeding:**

#### **Pharmacologic therapy:**

Nonselective beta-blockers (nadolol and propranolol) are the first line treatment for primary prophylaxis. They block vasodilatory beta-adrenergic receptors, permitting unopposed alpha-adrenergic

vasoconstriction in the mesenteric arterioles, thereby reducing portal venous inflow and pressure. They also decrease cardiac output, which further decreases the portal inflow.

Meta-analysis of clinical trials shows that the risk of bleeding is reduced by beta-blocker therapy versus placebo from 25% to 15% (62). The effectiveness of beta-blockers is most accurately assessed by the HVPG. The best predictor of success is a sustained decrease in the HPVG to less than 12 mm Hg, whereas patients who have a sustained 20% decrease in HPVG to greater than 12 mm Hg have a risk of bleeding of less than 10%. This approach is not widely applied to clinical practice. The efficacy of beta-blockers is clinically monitored by a decrease in the resting heart rate greater than 25% but not to a rate less than 55 beats/min. Only 20% to 30% of subjects achieve these endpoints, and 15% to 20% of subjects cannot tolerate and require discontinuation of this therapy.

Short-acting (nitroglycerin) or long-acting (isosorbide mononitrates) nitrates cause venodilatation, rather than arterial dilatation, and decrease portal pressure predominantly by decreasing portal venous blood flow. The effect on intrahepatic resistance is not impressive, and nitrates are no longer recommended for primary prophylaxis

Other agents that may decrease intrahepatic resistance include alpha adrenergic blockers and angiotensin II receptor antagonists. Prazosin, alpha adrenergic blocker, caused worsening of the systemic hyperdynamic circulation and was associated with portal hypertension and consequent sodium retention and ascites (63). Losartan, an angiotensin II receptor antagonist, caused a reduction in portal pressure without significant effects on the systemic circulation (64). It did not significantly reduce portal pressure in randomized controlled trials, but it worsened the renal function.

### **Endoscopic sclerotherapy:**

Prophylactic endoscopic sclerotherapy (EST) was used in the 1980s. Initially reported that it significantly reduced the risk of a first variceal bleed and improved survival, subsequent trials did not show a survival benefit. So EST is not recommended for prophylaxis of esophageal varices.

**Endoscopic variceal ligation:**

In comparison to no therapy, in patients with moderate-to-large esophageal varices, prophylactic endoscopic banding leads to a significant reduction in the incidence of first variceal bleeding and improves survival (65). Prophylactic banding has been compared with nonselective beta-blockers in several randomized controlled studies, and two meta analyses showed that prophylactic banding is more effective than beta-blockers in preventing the first variceal bleeding in patients with moderate-to-large esophageal varices, but it offers no survival advantage over nonselective beta-blockers (65).

In summary, nonselective beta-blockers or EVL are recommended first line treatments for primary prophylaxis of variceal hemorrhage. EVL may be used in subjects who cannot tolerate beta-blockers (eg, patients who have low blood pressure or asthma) and who have medium-large varices, whereas they preferentially use beta-blockers when the varices are small and technically difficult to band.

**Treatment of acute variceal bleeding:****Initial management:**

The management of acute variceal bleeding includes hemodynamic resuscitation, general treatments, prevention of complications, and achievement of hemostasis. Intravenous access must be promptly secured. Airway intubation is indicated in patients who are bleeding severely or who have mental status changes that preclude their ability to protect their airway. Intravascular volume loss is estimated and replaced with crystalloids and packed red cells.

The systolic blood pressure should be maintained at least at 90 to 100 mm Hg, and the heart rate should be maintained below 100 beats/min, with a hemoglobin level around 9 g/dL (hematocrit of 25–30), because over transfusion can cause a rebound increase in portal pressure and precipitate early rebleeding (66). Fresh frozen plasma and platelets (particularly for a platelet count <50,000/ml) are

often used to correct a coagulopathy. They do not adequately correct the coagulopathy and can induce volume overload and rebound portal hypertension. The use of recombinant factor VII has been shown to improve hemostasis rates, but it did not improve survival (67).

Bacteremia is often present on admission for acute variceal hemorrhage. Common bacterial infections include spontaneous bacterial peritonitis, urinary tract infection, and pneumonia. Infections are associated with an increased risk of rebleeding and higher mortality, likely secondary to a further increase in resistance to portal flow, further splanchnic arteriolar dilatation, and further coagulopathy (68). The use of antibiotics in acute variceal bleeding has been shown to reduce the risk of rebleeding and mortality. Therefore, antibiotics should be given to all patients from admission. Norfloxacin, 400 mg/12 hours, is the first-choice because of its simpler administration and lower cost (69). In high-risk patients (hypovolemic shock, ascites, jaundice, or malnutrition) intravenous ceftriaxone recently has been shown to be better than oral norfloxacin in a randomized trial (70).

### **General measures for the management of active variceal hemorrhage:**

#### **Airway protection**

Endotracheal intubation if altered mental status or unconscious

Gastric aspiration

#### **Hemodynamic resuscitation**

Crystalloids and blood transfusion

Correction of coagulopathy and thrombocytopenia

#### **Antibiotic prophylaxis for spontaneous bacterial peritonitis**

Blood cultures and diagnostic paracentesis if ascites present

Third-generation cephalosporin intravenously and switch to oral

quinolones when patient is stable and GI tract is functional

#### **Renal support**

Maintain urine output >50 mL/h

Avoid nephrotoxic drugs

### **Metabolic support**

Inject thiamine when indicated

Monitoring blood glucose level

Monitor and treat for delirium tremens

Monitor and treat for acid base and electrolyte disturbances

### **Neurologic support**

Monitor mental state

Avoid sedation

## **Pharmacologic therapy:**

### **Vasopressin**

Vasopressin is an endogenous nonopeptide that causes splanchnic vasoconstriction by acting on V1 receptors located in arterial smooth muscle, reduces portal venous inflow, and reduces portal pressure. However, leads to systemic vasoconstriction in addition to splanchnic vasoconstriction. It has severe toxicity, including bowel necrosis, myocardial ischemia and infarction from vasoconstriction combining glyceril-trinitrate with vasopressin has reduced adverse effects and improved efficacy over vasopressin alone.

### **Somatostatin**

Somatostatin is a natural peptide that induces splanchnic vasoconstriction. It has a half-life in the circulation of 1 to 3 minutes. It decreases portal pressure and collateral blood flow by inhibiting the release of glucagon (71). It also decreases portal hypertension by decreasing postprandial blood flow. It lacks most of the cardiovascular adverse effects seen with vasopressin.

The usual dose is an initial bolus of 250 mg followed by a 250 mg/h infusion that is maintained



until the achievement of a 24-hour bleed-free period. Therapy may be maintained for up to 5 days to prevent early rebleeding. Very recently, the use of higher doses (500 mg/h) has been shown to translate into increased clinical efficacy in the subset of patients with more severe hemorrhage, demonstrated by the finding of active bleeding at emergency endoscopy (72).

### **Octreotide**

Octreotide is a somatostatin analog with longer half-life (80 to 120 minutes). This, however, is not associated with longer hemodynamic effects than somatostatin. It usually is given as an initial bolus of 50 mg, followed by an infusion of 25 or 50 mg/h. As with somatostatin, therapy can be maintained for 5 days to prevent early rebleeding.

### **Terlipressin**

Terlipressin is a long acting triglycyl-lysine derivative of vasopressin. It is transformed slowly to vasopressin by enzymatic cleavage. Because of this slow release to the active agent, terlipressin has significantly fewer adverse effects than vasopressin. It may be initiated at a dose of 2 mg/4 hours for the first 48 hours, and it may be maintained for up to 5 days at a dose of 1 mg/4 hours to prevent rebleeding (73). This is the only treatment that has been shown to improve prognosis of variceal bleeding in placebo-controlled randomized controlled trials and meta-analysis (73). It is also useful in hepatorenal syndrome. Thus the use of Terlipressin for variceal bleeding may prevent renal failure, which frequently is precipitated by variceal bleeding.

F-180, another long-acting V1a-selective vasopressin analog, also has been shown to prevent the increase in portal pressure caused by blood transfusion (74).

## **Endoscopic therapy**

### **Endoscopic sclerotherapy**

EST has largely been supplanted by EVL, except when poor visualization precludes effective band ligation of bleeding varices. Current evidence does not support emergency EST as first-line treatment of variceal bleeding (75). The technique involves injection of a sclerosant into (intravariceal)

or adjacent to (paravariceal) a varix.

Complications of EST occurring during or after the procedure include chest discomfort, ulcers (and ulcer-related bleeding), strictures, and perforation. The risk of ulcers can be reduced by prescribing sucralfate after EST.

### **Endoscopic variceal ligation**

EVL is the preferred endoscopic modality for control of acute esophageal variceal bleeding and for prevention of rebleeding. Varices at the gastroesophageal junction are banded initially, and then more proximal varices are banded in a spiral manner at intervals of approximately every 2 cm. Varices in the middle or proximal esophagus do not need to be banded. EVL is associated with similar but fewer complications than EST and requires fewer sessions to achieve variceal obliteration.

In summary, the first-line treatment for active esophageal variceal hemorrhage is a combination of pharmacologic treatment (ie, octreotide) and endoscopic treatment (EVL or EST) (76). About 80% to 90% of patients achieve hemostasis with first-line therapy; the remaining patients fail to achieve hemostasis or experience early rebleeding.

Within the first 6 hours, failure to control bleeding is recognized by (60) (1) transfusion requirement of more than four units of packed red cells and (2) the inability to maintain the systolic blood pressure greater than 70mmHg or to raise it by 20mmHg or to reduce the resting pulse to less than 100/min or to decrease it by 20 beats/min.

After 6 hours, early rebleeding is defined by hematemesis together with (1) reduction in systolic blood pressure by 20 mm Hg from the level at 6 hours, (2) increase in pulse rate by 20/min from the rate at 6 hours on two consecutive readings 1 hour apart, or (3) the need to transfuse two or more units of packed red cells to increase the hematocrit to more than 27% or the hemoglobin to more than 9 g/dL.

Bleeding that occurs more than 48 hours after the initial admission for variceal hemorrhage and is separated by at least a 24-hour bleed-free interval is considered as rebleeding.

## **Factors affecting risk of continued bleeding or recurrent bleeding:**

### **Factors associated with failure to control acute hemorrhage**

- Spurting varices
- High Child-Pugh score
- High hepatic venous pressure gradient
- Infection
- Portal vein thrombosis

### **Factors associated with early rebleeding**

- Severe initial bleeding
- Overly aggressive volume resuscitation
- Infection
- High hepatic venous pressure gradient
- Complications of endoscopic therapy
- Renal failure

### **Factors associated with late rebleeding**

- High Child-Pugh score
- Large variceal size
- Continued alcohol use
- Hepatocellular carcinoma

In patients who have uncontrolled active bleeding or early rebleeding, definitive salvage therapy must be performed before the onset of complications related to the bleeding. Balloon tamponade effectively produces hemostasis in 80% to 90% of cases (77). Balloon tamponade requires airway protection, is associated with a high incidence of rebleeding when the balloon is deflated, and can cause pressure necrosis of the mucosa if the balloon remains inflated for more than 48 hours. It is therefore

used to temporize until definitive treatment is instituted. EVL can be attempted once more for early rebleeding. The salvage treatment in these patients is portal decompression, with transjugular intrahepatic portosystemic shunts (TIPS) being the procedure of choice.

### **Transjugular intrahepatic portosystemic shunts**

TIPS reduces elevated portal pressure by creating a communication between the hepatic vein and an intrahepatic branch of the portal vein. It produces hemostasis in more than 90% of cases (78). Once complications from bleeding of aspiration pneumonia or multiorgan failure occur, the prognosis is dismal regardless of the achievement of hemostasis. The best predictor of mortality after TIPS is the MELD (Model of End Stage Liver Disease) score.

Contraindications to TIPS include severe congestive heart failure, severe pulmonary hypertension, severe hepatic failure, portal vein thrombosis with cavernomatous transformation, and polycystic liver disease.

#### **Causes of bleeding and recurrent PHT after TIPS:**

- Stent dysfunction
  - Thrombosis
  - Retraction
  - Stenosis
  - Displacement
- Severe right-sided heart failure
- Hemobilia
- Persistent gastric varices
  - Associated with spontaneous splenorenal collaterals
  - Associated with massive splenomegaly

## **Surgery**

Surgical options include selective portosystemic shunting, calibrated H grafts, and devascularization procedures. The 30-day mortality rate, however, approaches 80% with these procedures. Therefore, in most situations, surgical intervention for acute variceal bleeding should be reserved for when medical therapy fails and TIPS is not available.

## **Secondary prophylaxis**

Once acute variceal bleeding is controlled, prevention of recurrent bleeding should be emphasized. After an index bleed, 70% of patients experience recurrent variceal hemorrhage within 1 year (79), and these patients have a 70% 1-year mortality.

The risk of rebleeding is greatest within the first 6 weeks, with more than 50% of rebleeding occurring within 3 to 4 days.

Risk factors for rebleeding include severe initial bleeding as defined by a hemoglobin level less than 8 mg/dL, gastric variceal bleeding, active bleeding at endoscopy, and a high HPVG (80,81). Age greater than 60 years, large esophageal varices, severe liver disease, continued alcoholism, renal failure, and the presence of a hepatoma also increase the risk of rebleeding (80,82).

It is important to prevent recurrent hemorrhage, preserve liver function, maintain a normal renal function, prevent ascites, and avoid alcohol consumption to prolong survival.

Orthotopic liver transplant is the only treatment that achieves most of these objectives and prolongs long-term survival. During this waiting time, they are at risk for recurrent variceal hemorrhage and therefore require treatment to prevent this complication.

## **Pharmacologic Therapy**

The main goal of pharmacologic is to significantly reduce portal hypertension and to prevent

recurrent bleeding. More than a 20% reduction in portal pressure has been shown to significantly reduce the cumulative probability of recurrent bleeding from 28% to 4% in the first year and from 39% to 9% at 2 years (83). Recent studies have shown that despite adequate beta-blocker therapy, there are a percentage of patients that still have hepatic venous pressure gradients above 12 mmHg, which puts them at continued risk for variceal hemorrhage (84).

Several trials have demonstrated the efficacy of a nonselective beta-blocker compared with placebo in decreasing the risk of recurrent bleeding and improving survival (85). The addition of isosorbide mononitrate (ISMN) to a betablocker regimen appears to further reduce the rate of rebleeding

In addition, recent studies have shown that combination pharmacologic therapy may be superior to sclerotherapy and band ligation. Incidence of rebleeding was 25% over an 18-month period with combination medical therapy compared with 53% for sclerotherapy in Child-Pugh class A or B cirrhotics (86).

### **Endoscopic therapy**

Even though sclerotherapy has been shown to be effective in reducing recurrent variceal hemorrhage and appears to be equivalent to beta-blocker therapy, band ligation appears to have similar efficacy in decreasing recurrent bleeding, but fewer complications and higher survival rates. Therefore, for endoscopic therapy to prevent rebleeding, band ligation should be considered the procedure of choice. Combination band ligation with pharmacologic therapy may be the ideal treatment modality.

In a study by Lo and colleagues comparing band ligation alone with band ligation plus nadolol and sucralfate, rebleeding was reduced from 47% to 23% with combination therapy (87). A more recent study by Pena and colleagues comparing band ligation alone with band ligation plus nadolol, demonstrated that the rebleeding rate was reduced from 38% to 14% with the combination group (88).

In addition, post banding ulcers are common, and significant bleeding from these ulcers occurs in 2% to 5% of cases. Varices rebleeding rates potentially can be reduced further by adding antiulcer

therapy after endoscopic therapy.

## **Surgical Shunt and Transjugular Intrahepatic Portosystemic Shunt**

### **Procedures**

Portocaval or distal splenorenal shunts have been used in preventing recurrent variceal bleeding. A meta-analysis comparing distal splenorenal shunt with sclerotherapy found that shunt placement significantly reduced the rate of recurrent bleeding but also increased the incidence of encephalopathy and did not improve survival (89). Rebleeding after surgical shunts typically is caused by shunt thrombosis, which occurs usually within the first year. It is unusual for surgical shunts to thrombose beyond 1 year.

Similarly, with TIPS compared with endoscopic therapy the rebleeding rate was significantly lower with TIPS, 19% versus 47%, but the incidence of encephalopathy was higher with TIPS, 34% versus 19%, with no difference in survival(90). Rosemurgy and colleagues compared TIPS with a surgically placed H-graft shunt and observed that the frequency of rebleeding was significantly less in the surgical group (3% versus 16%), and the patients who had TIPS required frequent interventions to maintain shunt patency. Thirty-day mortality rates, however, were higher in the surgical group, 43% versus 15%(91).

Therefore, surgical shunts should be used to prevent rebleeding in patients who do not tolerate or are not compliant with medical therapy and have relatively preserved liver function. TIPS should be reserved for patients who have poor liver function and who have failed medical therapy.

In summary, the following regimen is recommended for secondary prophylaxis of esophageal variceal hemorrhage:

1. Eradication of esophageal varices by EVL (every 7–14 days until varices are eradicated) with concomitant use of nonselective beta-blockers (propranolol or nadolol).

2. Long-term endoscopic control and banding of recurrent varices every 3 to 6 months.
3. If EVL is unavailable or contraindicated, nonselective beta-blockers can be used alone.
4. TIPS is considered if pharmacologic and endoscopic therapy failed (recurrence of variceal hemorrhage despite at least two sessions of endoscopic treatment performed not more than 2 weeks apart).

Always consider liver transplantation if the patient is Child-Pugh B or C.

## **Gastric varices**

Gastric varices are rare but important sources for bleeding in patients who have portal hypertension. Gastric varices can be classified into gastro–esophageal varices (GOV) or isolated gastric varices (IGV) (92). GOV are classified further into GOV 1 (in continuity with esophageal varices and extend 2 to 5 cm below the gastroesophageal junction) or GOV 2 (esophageal varices extending into the fundus). IGV can be located in the fundus (IGV 1) or body/antrum (IGV 2). Gastric varices located in the gastric fundus (either GOV 2 or IGV 1) carry a greater risk of bleeding than those located in other parts of the stomach (92).

The prevalence of gastric varices is 5% to 33% in patients who have portal hypertension, with an overall incidence of bleeding ranging from 3% to 30% (92). Mortality associated with gastric variceal hemorrhage is 30% to 53%, with a 30% rebleeding rate. Because GOV1 constitutes an extension of esophageal varices along the lesser curvature of the stomach, it is managed like esophageal varices. IGV1 secondary to splenic vein thrombosis is treated by splenectomy. There is no consensus on primary prophylaxis of bleeding GOV2 or IGV due to limited data.

GOV1 disappears in approximately 58% and 70% after EST and EVL of esophageal varices, respectively. The obliteration of varices at the gastroesophageal junction blocks the shunting veins in the palisade zone, leading to dilatation and the formation of new or secondary gastric varices. These



secondary varices occur at a rate of 9.7% to 15.3% and have a higher frequency of bleeding compared with primary gastric varices.

EST controls active bleeding in 40% to 100% of cases of GOV1. The primary drawback is the high risk of recurrent bleeding. EST is frequently associated with ulceration, which bleeds in approximately 50% of cases(93). Rebleeding rates have been reported to be 5.5% in GOV1, 19% in GOV2, and as high as 53% in IGV1(93).

EVL has been shown to achieve hemostasis rates of up to 89%, with a rebleeding rate of 18.5%. The major concern after gastric EVL is the potential of partial ligation of large gastric varices, which may produce bleeding. EVL is generally not recommended for IGV1.

Compared with EST or EVL, endoscopic variceal occlusion with tissue adhesives, such as N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate, or thrombin, is more effective for acute fundal gastric variceal bleeding . Successful obliteration leads to better control of the initial hemorrhage and lower rebleeding rates. TIPS is the major salvage or, perhaps, is even a primary therapeutic modality for gastric varices, with bleeding control rates greater than 90%.

Balloon-occluded retrograde transvenous obliteration is a newly developed transvenous sclerotherapy technique performed for treating gastric fundal varices from spontaneous gastroduodenal shunts(94) Shiba and colleagues(95) recently showed that balloon-occluded injection sclerotherapy is safe and effective even in patients who do not have gastroduodenal shunts.

### **Ectopic varices**

Ectopic varices are defined as portosystemic shunts, resulting from portal hypertension, that occur at any site in the gut or abdomen except in the gastroesophageal region. These sites include the duodenum, jejunum, ileum, colon, rectum, biliary tree, and ostomy sites.

Ectopic varices account for 1% to 5% of all variceal bleeding (96). Patients who have ectopic variceal hemorrhage typically present with sudden, profuse melena or haematochezia.

**Duodenal varices:**

Duodenal varices occur in about 0.4% in all patients with portal hypertension and account for one third of bleeding episodes from ectopic varices. The duodenal bulb is the most common site of duodenal varices, the second portion of the duodenum appears to be the next most common site but duodenal varices in the other portions are rare.

Hashizume et al. studied these varices angiographically and histopathologically; and found that the duodenal varix consisted of a single vessel with afferent and efferent vessels, forming a portosystemic shunt in the retroperitoneum. The varix traversed the duodenum and was present in the submucosal layer of the posterior wall; while the afferent vessel was the superior or inferior pancreaticoduodenal vein originating in the portal vein trunk or superior mesenteric vein, and the efferent vein drained into the inferior vena cava. They have also been reported at the site of previous duodenal operations and the resultant adhesions and after endoscopic sclerotherapy. Duodenal varices are more common in patients having extrahepatic portal vein obstruction and in those with thrombosed porto systemic shunts.

Apart from endoscopy, hypotonic duodenography, ultrasonography, computed tomography, venous phase of superior mesenteric angiography, and percutaneous transhepatic portography have been used to diagnose duodenal varices.

Medical therapies, including vasopressin and octreotide may have limited success in controlling active duodenal variceal bleeding. Endoscopic sclerotherapy(97) or with an occluding agent(98) are the main treatment modalities. Embolization and transjugular intrahepatic portosystemic shunt are the therapeutic alternatives, if endoscopic sclerotherapy or variceal ligation fails to control the bleeding. When conservative measures cannot control the hemorrhage, emergency laparotomy may be indicated. Duodenal varix suture ligation or resection results in a high rate of rebleeding. End-to-side portacaval shunt may be effective. An arteriovenous fistula requires resection of the para mural varix and surgical

occlusion.

### **Jejunal and ileal varices:**

A triad of portal hypertension (generally due to liver cirrhosis), history of abdominal surgery, and haematochezia without hematemesis characterizes small intestinal varices. Bleeding from varices may present with vesical varices and gross hematuria if an intestinal segment is used for an augmentation cystoplasty.

A history of abdominal surgery appears to predispose the development of ectopic varices (portosystemic communication) in adhesions. Possible physiological origins of this entity were studied in Edward's demonstration of network of fine communication between the parietal surface of the viscera and the posterior abdominal wall, arising in the embryo due to the juxtaposition of the developing systemic and visceral venous plexus. Formation of collaterals, de novo, is unlikely if the anatomy is undisturbed. In some cases no cause can be found. Although rare, bleeding from small bowel varices is associated with a high mortality as accurate preoperative diagnosis is often difficult.

Detection of these varices has been a challenging task and several invasive diagnostic techniques such as enteroclysis, Tc-99m RBC studies, venous phase of mesenteric arteriography, enteroscopy, color flow Doppler ultrasound and magnetic resonance angiography have been used for this purpose. Intraoperative Sonde enteroscopy is safe and effective, providing complete visualization of the small-bowel mucosa without enterotomy while avoiding the trauma that can be caused by push endoscopy. It is the diagnostic assessment of choice.

Medical therapy, including vasopressin infusion via the superior mesenteric artery, is often useful in controlling acute variceal bleeding. Percutaneous transhepatic embolization and transjugular intrahepatic portosystemic shunt are the therapeutic alternatives. Surgical treatment consists of lysis of adhesions and bowel resection combined with portosystemic shunt, under the presumption that the portal pressure in these patients has been partially decompressed through these spontaneous shunts and may increase significantly after their surgical division.

**Colonic varices:**

Colonic variceal bleeding is a rarity and is most commonly due to portal hypertension, with local mesenteric vein obstruction constituting a rare cause. The true prevalence of colonic varices is not known, but Feldman et al. found an incidence of 0.07% in autopsy material. Esophageal varices were present in approximately half of the group with colonic varices. Bleeding has been reported to occur in 2.5% of patients attending sclerotherapy sessions for esophageal varices. In patients with portal hypertension the coronary azygous system was the primary portosystemic channel in at least half of the cases, but in a quarter of cases it was the inferior mesenteric-internal iliac system.

Possible etiologies of this condition may be esophageal transection and devascularization and extensive thrombosis of the portal vein resulting in obliteration of the coronary-azygous anastomotic system. In such a situation, other potential sites of porto-systemic anastomoses, such as that in the colon, may open, leading to development of colonic varices. Idiopathic/primary, familial, secondary to splenic vein thrombosis and adhesion-related colonic varices without portal hypertension have also been reported.

Varices of the colon are usually segmental, involving predominantly (66%) the distribution of inferior mesenteric vein and less frequently (26%) the distribution of superior mesenteric area, and never confined to transverse colon. Diffuse variceal involvement of the colon is uncommon and implies an unknown cause.

Colonoscopist visualizes these varices as serpiginous to nodular, often bluish submucous lesions. They are often missed on colonoscopy due to collapse of varices during periods of hypotension or because of increase in the intraluminal pressure due to air insufflation during the endoscopic examination. Sensitivity of colonoscopy is greatly reduced during periods of active bleeding and in the absence of good bowel preparation.

In cases where the cause of lower GI bleeding is not clear, even after colonoscopy; venous phase of mesenteric angiogram and scintigraphic studies may be useful. If doubt persists, intraoperative colonoscopy may be useful to pinpoint the problem.

Conservative therapy consists of vasopressin and somatostatin analogue, which may be useful in the control of bleeding. Sclerotherapy using a colonoscope and transjugular intrahepatic portosystemic shunt are other therapeutic alternatives.

The choice of surgical therapy in portal hypertension is portal decompression and not colonic resection; as colectomy is associated with significantly greater mortality due to risk of infection and considerable technical difficulty of this surgery in the presence of portal hypertension.

#### **Anorectal varices:**

Anorectal varices are a rare cause of rectal bleeding and are often erroneously diagnosed as bleeding hemorrhoids. Although rare, rectum is the most common site of lower gastrointestinal varices. Rectal varices occur due to high pressure in the inferior mesenteric venous system in patients with portal hypertension. Bleeding from them is uncommon, and often mild and self-limiting, but rarely it can be fatal.

The reported incidence of rectal varices ranges from 40 to 89.3%. No correlation has been found between the presence of anorectal varices and the Child's grade of cirrhosis, intrahepatic V/s extra hepatic causes of portal venous obstruction, the grade of esophageal varices, the presence of gastric varices, portal hypertensive gastropathy, or whether or not patients received sclerotherapy.

Identifying the source of lower gastrointestinal hemorrhage in patients with chronic liver disease and portal hypertension can be challenging but the differential diagnosis between hemorrhoids and anorectal varices has been elucidated in many studies. It has also been documented that the

prevalence of hemorrhoids is not increased in patients with portal hypertension and their presence is unrelated to the degree of portal hypertension.

Anorectoscopy is the initial investigation of choice. Rectal endoscopic ultrasonography, transvaginal sonography and magnetic resonance imaging are useful in detecting the presence and number of rectal varices.

The principal emergency treatment is endoscopic sclerotherapy or endoscopic ligation, failing which surgical ligation should be performed. Before the advent of transjugular intrahepatic portosystemic shunt (current choice of treatment), a portosystemic shunt, preferably between the inferior mesenteric vein and the vena cava or renal vein, was the treatment of choice. Transjugular embolization of the inferior mesenteric vein is an alternative to TIPS, where TIPS is not feasible.

### **Biliary varices:**

Gallbladder varices are often seen in portal hypertension, more often in extra hepatic portal vein obstruction patients. Gallbladder varices do not correlate with size of esophageal varices, number of sessions of sclerotherapy, presence or absence of gastric varices, portal gastropathy, Child Pugh grade or splenorenal shunt placement. These collaterals cause some gallbladder stasis but do not impede gallbladder function and hence seem unlikely to contribute to gallstone formation. Their clinical significance is their propensity to bleed during biliary surgery; thus, the operating surgeon should be aware of them. The color flow Doppler is the gold standard procedure for the diagnosis, although angiography, computerized tomography and magnetic resonance have also been reported.

Bile duct varices are seen more frequently in left hepatic duct, possibly due to the joining of umbilical vein to the left branch of portal vein adjacent to the left hepatic vein. Due to their propensity to bleed, balloon dilatation is probably best avoided in these patients and placement of pigtail biliary endoprotheses is preferred over straight stents with side flaps. Usually biliary varices are found incidentally during imaging, but their presence calls for a search for portal vein thrombosis. Rarely they

can give rise to obstructive jaundice or haemobilia

### **Stomal varices:**

Variceal bleeding from enterostomy is an unusual complication of portal hypertension and represents a cause of recurrent or intractable gastrointestinal bleeding. Presence of caput medusae/varices developing around a stoma may herald the presence of mild to moderate portal hypertension before other signs of hepatic decompensation are evident. Once variceal communications have been formed between the portal venous system of the gut and subcutaneous systemic circulation, heavy bleeding from dilated venous plexus may occur spontaneously or from microtrauma.

Proper diagnosis requires careful inspection of the muco-cutaneous region of the stoma for venous bleeding sites and endoscopy examination of the stoma to rule out the presence of recurrent bowel disease or other lesions like arteriovenous malformations, polyp or Crohn's disease.

The emergent treatment of bleeding of the colostomy must combine several methods, quite often consecutively: local compression, ligation, and sclerotherapy. Palliative local measures, like suture ligation or sclerotherapy, however, remain the treatment of choice in the high-risk, cirrhotic patient who is unlikely to survive a major operation and may increase the interval between bleeding episodes and decrease the severity of bleeding. The hemorrhage can be managed temporarily in most patients with local measures. Once bleeding is controlled, the treatment must be primarily medical (hygienic and dietary habits,  $\beta$ -adrenergic blocking agents), but complementary surgery is invariably necessary because of recurrence of bleeding.

There is no consensus on which of the various surgical options is best, but mucocutaneous disconnection is simple, quick, repeatable and associated with a lower morbidity and intraoperative blood loss than stomal relocation. It should be kept in mind that repeated use of local operative procedures leads to the formation of scar tissue and causes problems in the care of the stoma. Although

stomal manipulation is the most commonly performed procedure, portosystemic shunting has the lowest incidence of both rebleeding and need for additional procedures and provides the longest mean postoperative survival and is the choice in patients who are good surgical candidates. Transjugular intrahepatic portosystemic shunt and stomal varices embolization are effective alternatives in case of recurrent bleeding of stomal varices.

The overall prognosis mainly depends on the function of the liver, the deterioration of which is accelerated by the successive hemorrhagic accidents. Particular attention should be paid to stoma care and the prevention of trauma from appliances.

### **Gastric antral vascular ectasia**

Gastric antral vascular ectasia (GAVE), or watermelon stomach, describes a vascular lesion of the gastric antrum that consists of ectatic and sacculated antral mucosal vessels radiating toward from the pylorus. Its cause is unknown, but it has been proposed that gastric peristalsis causes prolapse of the loose antral mucosa into the duodenum with consequent elongation and ectasia of the mucosal vessels. Microscopic features include dilated capillaries with focal thrombosis, dilated and tortuous submucosal venous channels, and fibromuscular hyperplasia of the muscularis mucosa.

Most cases are idiopathic, but it has been associated with cirrhosis, achlorhydria, atrophic gastritis, and the CREST syndrome and has occurred after bone marrow transplantation. The association with cirrhosis and portal hypertension is considered unreliable because GAVE with coexisting portal hypertension does not generally respond to reduction of the portal pressure. GAVE may cause acute hemorrhage or chronic occult bleeding.

It frequently occurs in middle-aged or older women. Treatment consists mainly of endoscopic coagulation with heater probe, Gold probe, argon plasma coagulator, or laser therapy. Chronic cases sometimes require periodic transfusions and iron therapy. Portal decompression with TIPS does not reduce the bleeding. Antrectomy prevents recurrent bleeding but is usually reserved for patients who



fail endoscopic therapies.

### **Portal hypertensive gastropathy**

Portal hypertensive gastropathy (PHG) is characterized endoscopically by three patterns: (1) fine red speckling of gastric mucosa; (2) superficial reddening, especially on the tips of the gastric rugae; and, most commonly, (3) the presence of a mosaic pattern with red spots (snake-skin appearance) in the gastric fundus or body.

Histologically, the stomach in PHG contains dilated, tortuous, irregular veins in the mucosa and submucosa, sometimes with intimal thickening, usually in the absence of significant inflammation. PHG is correlated with the severity of liver disease. It is diagnosed by endoscopy. It is an uncommon cause of significant UGI bleeding in patients who have portal hypertension. Acute bleeding from PHG was observed in only 2.5% of patients.

Treatment is directed at decreasing portal pressure. Propranolol has been shown to significantly reduce the rate of recurrent bleeding compared with placebo (35% versus 62% at 1 year) (92). Vasopressin, terlipressin, somatostatin, and octreotide have not been studied for this indication. TIPS is the next therapy. It is associated with significant improvement in the endoscopic findings and a decrease in the transfusion requirements. If bleeding continues, surgical portal decompression is performed. Liver transplantation is indicated for decompensated liver disease. Endoscopic thermal coagulation is not effective for controlling or preventing this diffuse form of bleeding.

### **Downhill varices**

Esophageal veins form a plexus on the outer surface of the esophagus. The lower part drains into the short and left gastric veins of the portal system, whereas the upper part drains into the azygous, thyroid, and internal mammary veins and then into the superior vena cava.

“Downhill” esophageal varices (DEV) form in the upper third of the esophagus as collateral branches directing blood flow “downward” to bypass superior vena cava (SVC) obstruction via the azygous vein or to drain the systemic superior venous system via the portal vein when the SVC and the

azygous vein are obstructed.

DEV are mostly due to SVC syndrome secondary to mass effects (external compression of the SVC) from lung cancer, intrathoracic goiter, mediastinal lymphoma, thyroid carcinoma, thymoma, or mediastinal lymphadenopathy secondary to head and neck cancers. DEV usually disappear after treatment of the underlying condition. Several cases have been associated with gastrointestinal hemorrhage, which can be life threatening.

## MATERIALS AND METHODS

Consecutive patients presenting with bleeding esophageal varices for the first time between January 2006 and December 2006 and registered in the liver clinic of the Institution were included in the study. Those patients with an earlier variceal bleed and on EST schedule, initiated elsewhere were excluded from the study. Childs C patients who failed to recover and presented with variceal bleed were also excluded.

Patient details at the time of registration were recorded in a pre-structured proforma. Details included address, cell number, age, gender, etiology of portal hypertension, Child-Pugh Score. The latter was applied to grade the severity of cirrhosis. This was based on serum bilirubin, serum protein, ascites, prothrombin time and encephalopathy (Table 1).

**Table 1 Child-Pugh Score:**

Based on scoring system, cirrhosis was classified as Childs A when the total score was 5 and 6,

<b>Variables</b>	<b>Childs A</b>	<b>Childs B</b>	<b>Childs C</b>
<b>Serum bilirubin</b>	<b>&lt; 2 mg%</b>	<b>2 -3 mg%</b>	<b>&gt; 3 mg%</b>
<b>Serum albumin</b>	<b>&gt; 3.5 g%</b>	<b>2.8 – 3.5 g%</b>	<b>&lt; 2.8 g%</b>
<b>Ascites</b>	<b>Nil</b>	<b>Mild</b>	<b>Moderate / Severe</b>
<b>Prothrombin time</b>	<b>&lt;14 sec</b>	<b>15 – 17 sec</b>	<b>&gt; 18 sec</b>
<b>Encephalopathy</b>	<b>Nil</b>	<b>Mild / Moderate</b>	<b>Moderate / Severe</b>

Childs B when the total score was 7 to 9 and Childs C when the total score was 10 to 15.

Bleed details included date of index bleed, subsequent bleed until eradication, details of EST such as grades of varices, features of imminent bleed, nature and volume of sclerosant used and number of sessions required to obliterate the varices. The protocol for variceal injection followed by the department was as follows. 14 to 18 ml of 1% sodium tetradecyl sulphate was used to inject the varices in the first sitting. All patients were admitted for a day and were on prophylactic parenteral ciprofloxacin 200 mg 1 hr prior to the EST session. EVL was not available at all times and hence only those cases on regular EST were included for the study.

The varices were injected both intravariceal and paravariceal close to the gastro oesophageal junction using 23 gauge needle. For larger varices Gr III and IV paravariceal was followed by intravariceal injection. The second and subsequent injections were done at three weekly intervals until eradication of varices. The end point was sclerosed varices. The number of sessions and complications if any during or after the procedure were noted. Injection was deferred in those patients who had odynophagia, chest pain, and esophageal ulcers or had fever or focus of infection. Those patients who had a bleed in between the recommended sessions had an EST at that point of time. Patients with large fundal varices were excluded from the study. Devascularisation with or without shunt is the recommended protocol of management for these patients in our Institution.

All patients were on secondary prophylaxis with propranolol 40 mg twice a day or until the pulse rate decreased by 25% of the baseline rate.

Follow up protocol of eradicated varices included rescope for variceal recurrence at 3 monthly intervals until March 2008. Eradication of varices was defined as the absence of varices on subsequent endoscopy examination during follow-up visits.

The grades of varices, signs of imminent bleed such as red wale sign, cherry red spots and

hematocystic spots were noted. Details of bleed after eradication i.e. defined as rebleed were noted and sclerotherapy was done as per the protocol. The end point of the study was the first bleed after eradication. Further EST was done for residual or recurrent varices.

## OBSERVATION AND RESULTS

133 consecutive patients were treated for esophageal variceal bleeding and were registered between January 2006 and Dec 2006. There were 86 men and 47 women (mean age:  $45.51 \pm 11.8$  years; age range, 20 to 77 years). A total of 611 EST sessions were performed with a mean of 4.6 injections.

43(32.3%) of the 133 patients continued to have recurrent bleed in between the EST sessions and eradication of varices. 16 (12%) patients died within 3 months of registration, 8 from massive GI bleed, 4 from hepatic encephalopathy, 2 from hepatorenal syndrome and 2 from spontaneous bacterial peritonitis. They had overall 28 EST sessions with a mean of 1.8 injections.

Of the 39(29.3%) patients who did not complete the study, 26 (19.5%) were lost to follow up. They had had 89 EST sessions with a mean of 3.4 injections. In 13 patients oesophageal varices persisted at the end of 6 months despite repeated EST session (mean: 9.4 injections). Six patients died during the interim period due to hepatic encephalopathy (4 pts) and hepatorenal syndrome (2pts). Three patients required elective surgery (Revascularization). Four patients declined regular long-term follow-up and further injection therapy.

The 133 patients received a total of 611 emergency and elective injection treatments during the study period. Minor complications of sclerotherapy consist of transient fever and chest pain.

Esophageal mucosal ulceration at the injection site was found on 128(20.9%) occasions in 62

patients. Subsequent sclerotherapy was delayed in patients who had mucosal ulceration in greater than one quadrant of esophageal circumference.

A contained injection leak occurred on 2 occasions in 2 patients and was treated with intravenous antibiotics and nasogastric tube feeding.

A esophageal stricture at the injection site occurred in 4 patients after sclerotherapy. One patient required esophageal dilation, with complete relief of symptoms after dilation.

**Tab 2 Complications in 133 patients**

**Figure 1. Eradication and recurrence of esophageal varices**

133patients	
Type of complication	Complications per sclerotherapy (%)
Esophageal ulceration	128 (20.9%)
Injection site leak	2 (0.3%)
Stricture	4 (0.7%)
Completed the study (Varices eradicated) 78 (85.7%)	Not completed the study - Dead 16(12%) - Others 39(29.3%)





Majority of the patients had alcohol related cirrhosis (42.3%), followed by HBV related cirrhosis (19.2%). In 22 patients, the cause remained unknown (28.2%).

There were 48 men and 30 women. The mean age for men was  $41.2 \pm 11.8$  yrs and for women was  $48.1 \pm 11.76$  years. Minimum period of follow up of obliterated esophageal varices was for 12 months and the longest follow up was for 22 months. Eradication of varices was possible after a median of 4.77 injections.

**Tab 4**

Month of registration	Total no.	Eradicated varices	No. of inj	Follow up period (mo)	Recurrences	Grades – varices			Rebleed	Grades - varices			Dead
						1	2	3		2	3	4	
Jan-Mar 2006	32	17	4.8	21.5	9	3	5	1	4	0	2	2	2
Apr-Jun 2006	35	23	5	18	11	5	5	1	3	1	1	1	0
Jul-Sep 2006	29	16	4.5	15.8	8	2	4	2	2	0	1	1	1
Oct-Dec 2006	37	22	4.8	12	13	5	6	2	5	1	2	2	2
Total	133	78	4.8	16.8	41	15	20	6	14	2	6	6	5

Table 4 and the Figure 1 summarises the study group and the follow up for recurrence of varices and bleed rates after obliteration.

### **I. Recurrence of varices, bleed rates and bleed related mortality:**

32 cases were registered in the first quarter i.e. between Jan to March 2006. 17 had eradication of varices after the mean of 4.8 sessions. 9 patients (52.9%) had recurrence of varices on follow up of 21.5 months. The grades of varices were I, II and III in 3 (33.3%), 5 (55.5%) and 1 (11.1%) respectively. Four patients (44.4%) bled during the follow up period. One of the two deaths was due to variceal bleed.

Of the 35 cases registered in the second quarter (between Apr to Jun ) 23cases had eradicated the varices by October after a mean of 5 EST sessions. These patients could be followed up for 18 months. Of the 11 (47.8%) who had recurrence of varices, 5(45.5%) had Gr I varices, 5 (45.5%) had Gr II varices and one (9.1%) had Gr III varices. Three patients (27.3%) had a variceal bleed. There were no bleed related deaths.

After eradication, bleed occurred in 3(27.3%) patients.

Of the 29 cases registered in the third quarter (between Jul to Sep 2006), 16 had varices eradication after a mean of 4.5 injection. Follow up for 15.8 months after eradication, showed recurrence of varices in 8 (50%), 2 of whom i.e. 25% had Gr I and Gr III and 4 (50%) had Gr II varices. Two patients had variceal bleed after eradication.

Of the 37 cases registered in the fourth quarter 22 cases had varices eradication within 4 months of registration after a mean of 4.8 variceal injections. On follow up at 12 months after eradication, 13 (35.1%) had recurrence of varices, amongst whom 5 (38.4%) had grade I varices, 6(46.1%) had grade II varices and 2 (15.4%) had grade III varices. Bleed after eradication occurred in 5 (38.4%) patients; one of the two deaths was due to variceal bleed.

Summarising, of the 41 variceal recurrences, majority i.e. 32 (78%) patients had recurrence of

varices within 6 months of follow up and the rest subsequently. Also majority of rebleed occurred within 3 months i.e. in 11 patients (78.6%) and the rest later.

Month of registration	Eradicated varices	Follow up period (mo)	Recurrence	Recurrences (mo)			Rebleed (mo)		
				0-3	3-6	6-24	0-3	3-6	6-24
Jan-Mar	17	21.5	9	3	5	1	2	2	-
Apr-Jun	23	18	11	4	4	3	2	1	-
Jul-Sep	16	15.8	8	2	3	3	3	-	-
Oct-Dec	12	12	13	6	5	2	4	-	-
Total	78	16.8	41	15	17	9	11	3	-

**Tab 5**

There were 27 (65.9%) non bleeders. The grades of varices were I, II and III in 7 (26%), 15 (55%) and 5 (19%) respectively. Ten (27%) patients died, 5 from hepatic encephalopathy, 3 from hepatorenal syndrome and 2 from spontaneous bacterial peritonitis. 17 (63%) patients were alive at the end of the study.

## **II. Non recurrence of varices, bleed rates and bleed related mortality:**

In 37 of the 78 (47.3%), the varices remained eradicated until the end of follow-up. 12 (32.4%) patients died, 6 from hepatic encephalopathy, 4 from hepatorenal syndrome and 2 from spontaneous bacterial peritonitis.

## DISCUSSION

Bleeding from esophageal varices is the leading cause of death in patients with portal hypertension, with a mortality of up to 50% for the initial bleed and 30% for subsequent bleeds (1-4). The greatest risk is during the first 72 hrs and more than 50% of all early rebleed episodes occur within the first 10 days after cessation of active hemorrhage (23).

The most common source of recurrent bleeding before variceal eradication are from residual patent varices. This was 32.3% in the present series, a figure similar to that reported by Krige et al (99). Emergency endoscopy is essential since in 85.9% of patients with recurrent bleeding, the source is invariably the varices. These can be optimally treated by sequential EVL or sclerotherapy.

Overall, the esophageal varices remained eradicated in 37 (47.3%) patients after a follow up period of one year. Although new varices formed following initial obliteration in 41(52.6%) of the 78 patients, this was associated with varices related rebleed in 14 patients (34.1%), a figure similar to that reported by Krige et al (37.5%) (99). Of the 41 variceal recurrences, majority i.e. 32 (78%) patients had recurrence of varices within 6 months of follow up and the rest subsequently. Also majority of rebleed occurred within 3 months i.e. in 11 patients (78.6%) and the rest later.

The present study evaluated the complications occurring in 133 patients undergoing emergency and elective sclerotherapy. Complications were mostly minor and occurred in half of patients similar to Krige et al (99). Our figure of 20.9% corresponds to the 20-23% reported in earlier series by Westaby et al (100). This is in contrast to the 39.4% reported by Krige et al (99), who performed EST sessions at weekly intervals

Asymptomatic esophageal ulceration at the injection site was the most common complication

and was detected at follow-up endoscopy. Ulcers are generally considered an inevitable temporary consequence of the sclerosant, occurring after frequent or large-volume injections.

In most patients in this study, mucosal ulceration healed without sequelae. Our present policy is to use lower volumes of sclerosant as varices decrease in size in an attempt to reduce the extent of ulceration.

Endoscopic variceal ligation has now replaced injection sclerotherapy in the elective treatment of esophageal varices. Data from randomized controlled trials show more rapid eradication of varices with lower rates of recurrent bleeding and fewer complications such as strictures and perforation (31). However, a recent survey by the American College of Gastroenterology International GI Bleeding Registry shows that sclerotherapy is still used as frequently as banding for endoscopic intervention during index bleeding and more frequently than banding for control of variceal rebleeding. Likely reasons include convenience, cost, and widespread availability. It is noteworthy that several recent randomized controlled trials comparing band ligation with sclerotherapy have reported a higher recurrence rate of varices in patients undergoing band ligation.

Our current management policy is to have regular endoscopic therapy to achieve early variceal eradication, appreciating those factors such as esophageal ulceration and poor patient compliance may interfere with the endoscopic therapy program. After eradication of the varices, patients have surveillance endoscopy at 3 month intervals and, if recurrent varices are identified, a comprehensive endoscopic treatment schedule is instituted again.

Ultimately, the use of sequential combined endoscopic techniques with variceal banding initially when varices are large followed by sclerotherapy when varices are small may enhance the endoscopic management of esophageal varices in terms of reducing complications, facilitating earlier eradication, and preventing recurrence (101)

## **Summary and conclusion**

- 133 patients with variceal bleed due to cirrhosis with portal hypertension were registered between January 2006 and Dec 2006.
- A total of 611 EST sessions were performed with a mean of 4.6 injections for obliteration of varices.
- Complications related to injection sclerotherapy were mostly minor.
- 78 (58.6%) patients had variceal eradication by after a median of 4.77 injections by April 2007 and were followed up to March 2008.
- Varices recurred in 52.6% patients; 78% recurred within 6 months.
- Rebleed occurred in 34.1% and in 78.6% instances the bleed occurred within 3 months.
- In 37 patients the varices remained eradicated until the end of the study. Bleed related deaths were low after variceal eradication.

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# PROFORMA

**Name:**

**Age:**

**Sex:**

**MGE No:**

**Address:**

**Mobile No:**

**Final diagnosis:**

**Date of registration:**

**Aetiology:**

**Child Pugh Score:**

**Bleed details:**

	<b>Date</b>	<b>Interval between bleed</b>	<b>Hemodynamic status</b>	<b>Blood transfusion</b>	<b>EST</b>
<b>Index bleed</b>					
<b>2<sup>nd</sup> bleed</b>					
<b>3<sup>rd</sup> bleed</b>					
<b>4<sup>th</sup> bleed</b>					

5 <sup>th</sup> bleed					
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**Sclerotherapy details:**

	Date	Interval between bleed & EST	Grades of varices	Features of imminent bleed	Technique	Amount of sclerosant used	Complications
Index bleed							
2 <sup>nd</sup> bleed							
3 <sup>rd</sup> bleed							
4 <sup>th</sup> bleed							
5 <sup>th</sup> bleed							

**No.of EST till obliteration:**

**Recurrence of varices: YES / NO**

**Grade of varices after recurrence: I / II / III / IV**

**Bleed after recurrence of varices: YES / NO**

**Cause of death: HE / HRS / SBP / Massive bleed / HPS**

